REMARKS/ARGUMENTS

Claims 1, 2, 4-13, 15, 37-45 and 47 are pending in the present application. Claims 3, 14 and 46 have been cancelled. Claims 1, 4, 5, 13, 37, 39, 42, 44 and 45 have been amended. No new matter has been added.

Species Election

Applicants have amended claims 37, 39, 42, 44 and 45 to read on the elected species as suggested by the Examiner.

Priority Benefit Under 35 U.S.C. § 120

The Examiner contends states that the "subject matter claimed in Claims 3-5, 7, 39 and 45, that is a method of hematopoietic cells transplantation, wherein transition metal chelator is tetraethylpentamine does not have support in the parent applications Serial Numbers: 09/161,695, 09/130,367 and 09/024,195." The Examiner has asked that Applicants provide a detailed analysis demonstrating that the instant claims are entitled to the benefit under 35 U.S.C. § 120 of all the parent application filing dates. Applicants provide this analysis below.

The earliest parent application from which the present application claims priority under 35 U.S.C. § 120 is USSN 09/024,195 filed on February 17, 1998. In 09/024,195, a method of hematopoietic cells transplantation is described in the specification on page 9, lines 1-8. Additionally the 09/024,195 specification teaches that the hematopoietic cells may be obtained from, amongst others, neonatal umbilical cord blood (see page 9, lines 13-14; claim 20) and that the copper chelator may be tetraethylenepentamine (see page 7, line 12). Furthermore, the 09/024,195 application contains a claim (claim 18) directed to a method of hematopoietic cells transplantation comprising, amongst other steps, obtaining hematopoietic cells to be transplanted from a donor. Claim 20, of 09/024,195, recites that the hematopoietic cells is from a source which includes neonatal umbilical cord blood. Accordingly, the 09/024,195 specification adequately teaches the subject matter claimed in claims 3-5, 7, 39 and 45 of the present application. The priority claim to 09/024,195, is therefore proper.

The 09/130,367 application was filed August 7, 1998 and is a CIP of the 09/024,195 application. The 09/130,367 application also teaches a method of hematopoietic cells transplantation (see page 10, lines 12-19; page 24, line 5-page 26, line 8. The method of hematopoietic cells transplantation is also claimed in claim 18. Additionally the 09/130,367 specification teaches that the hematopoietic cells may be obtained from, amongst others, neonatol umbilical cord blood (page 10, lines 5-6; claim 20) and that the copper chelator may be tetraethylenepentamine (see page 8, line 21;).

The 09/161,695 application was filed September 29, 1998 and is a CIP of 09/130,367, which is a CIP of 09/024,195. The 09/161,695 application refers to co-pending applications 09/130,367 and 09/024,195 as teaching that chelating agent tetraethylpentamine inhibits cell differentiation (see page 6, lines 4-9). The 09/161,695 application further teaches the use of hematopoietic cells (see page 9, line 10; page 17, line 8-9) and that such cells may be obtained form neonatal umbilical cord blood (see page 9, lines 15-16; page 17, lines 14-15).

In view of the above, Applicants respectfully submit that the claimed subject matter in the present application has clear support in all the parent applications to which it claims priority benefit under 35 U.S.C. § 120. This objection should be withdrawn.

Additionally, as required by the Office Action, Applicants have amended the specification on page 1, line 15 to reflect the status of the parent applications 09/161,695, 09/130,367 and 09/024,195.

Drawings

The Examiner has stated that the submitted formal drawings fail to comply with 37 CFR 1.84 and requests that the Applicant review the enclosed PTO-948 form. Applicants submit herewith a complete set of Formal Drawings (Figures 1 - 27f) in compliance with 37 CFR 1.84.

Objections to Claims

Claims 1-15 and 37-47 are objected to because the word "copper" is misspelled in claims 1 and 37. Claims 1 and 37 have been amended to correct the spelling of the word copper. This objection should be withdrawn.

Rejection under 35 U.S.C. 112, First Paragraph

Claims 1-15 and 37-47 are rejected under 35 U.S.C. 112, first paragraph. The Examiner acknowledges that hematopoietic cells enriched for CD34+ cells are enabled in the claimed methods (*See*, Office Action at page 4). However, the Examiner contends that "the specification, while enabling for a method of hematopoietic cells transplantation and a method of adoptive immunotherapy, comprising a step of providing CD4+ (sic CD34+) ex vivo with conditions for cell proliferation and at the same time for reducing a capacity of said cells in utilizing copper, thereby expanding a population of said cells, while at the same time inhibiting differentiation of said cells does not reasonably provide **enablement** for a method of hematopoietic cells transplantation and a method of adoptive immunotherapy, comprising a step of providing *any* cells ex vivo with conditions for cell proliferation and at the same time for reducing a capacity of said cells in utilizing copper, thereby expanding a population of said cells, while at the same time inhibiting differentiation of said cells" (*See*, Office Action at page 4).

Claims 1 and 37, as amended, recite that the hematopoietic cells expanded *ex vivo* are enriched for CD_{34}+ cells.

As the Examiner has acknowledged, these amended claims are enabled. Therefore, Applicants respectfully request that the present rejection be withdrawn.

Rejections under 35 U.S.C. 103(a)

I. The Claims are Not Obvious over *Moore* or *De Bruyn* in view of *Cicuttine*

Claims 1-5, 8-15, 37 and 40-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moore et al, Blood Cells, 20: 468-481 (1994) ("*Moore*"); or C. De Bruyn et al., Stem Cells 13: 281-288 (1995) ("*De Bruyn*"); each in view of Cicuttine et al. Blood 80: 102-112 (1992) ("*Cicuttine*").

Obviousness requires that there be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant. (*In re Kotzab*, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000)). Additionally, all the claimed limitations must be taught or suggested by the prior art. (*In re Royka*, 180 U.S.P.Q. 580 (CCPA 1974)). Applicants submit

neither *Moore, De Bruyne* nor *Ciccutine*, alone or in combination teach or suggest the invention recited in the amended claims. Applicants have cancelled claims 3, 14 and 46. Thus this rejection, as it refers to these claims is moot and should be withdrawn. Applicants traverse this rejection as it applies to pending claims 1, 2, 4, 5, 8-13, 15, 37, 40-45 and 47.

Moore and *De Bruyn* both refer to hematopoietic umbilical cord blood derived progenitor cells obtained from a donor and have proved superior to adult marrow or peripheral blood in *ex vivo* cultures supplemented with only cytokines. Pending claims 1, 2, 4, 5, 8-13, 15, 37, 40-45 and 47 refer to a technology that slows the process of cell differentiation, therefore enabling superior expansion of progenitor cells as compared with the expansion of these cells in cultures treated with only cytokines. Neither *Moore* nor *De Bruyn* teach or suggest reducing the capacity of the hematopoietic cells in utilizing copper to inhibit differentiation during *ex vivo* expansion, as recited by the instant claims.

Cicuttine does not cure this fatal deficiency in *Moore* or *De Bruyn*. *Cicuttine* refers to a method of co-culturing hematopoietic progenitor cells with stromal cell lines and using zinc to control proliferation of the **stromal** cell line that is used for the co-culture. Specifically, *Cicuttine* attempts to establish spontaneous human stromal cell lines (SCL) to support expansion of hematopoietic progenitor cells in *ex vivo* conditions. However, attempts to establish human spontaneously cell lines had limited success. In his study, *Cicuttine* used a large T oncogene to immortalize stroma cells. Unfortunately, following transformation the stromal cells lost their contact inhibition, which is a prerequisite for co-culture with hematopoietic cells. *Cicuttine* overcomes this limitation by introducing the T oncogene under the control of a Zn-responsive element of a metallothionein promoter, whereby the promotor is switched on in the presence of Zn, and the stroma cells proliferate till confluence. The Zn is then washed out and the promotor is switched off and the stromal cells stop proliferating. Co-cultures (addition of hematopoietic cells to the stroma cells) are initiated following withdrawal of the Zn from the culture system. In this system Zn has nothing to do with hematopoietic progenitor cells (*See, Cicuttine* page 104, column 2, co-culture of CD34+ cells with SCL...) . As stated above, Zn in this system switched off the T oncogene controlling the transformation state of the stromal cells.

Cicuttine does not in any way refer to reduction of copper to inhibit differentiation of the **hematopoietic** cells during their *ex vivo* expansion. The Examiner suggests that "zinc has an affinity for copper" and refers to the discussion section in *Ciccuttine* (*See,* Office Action at page 6). Applicants have reviewed the discussion section of *Ciccuttine* and do not agree that there is support for that suggestion. Since both zinc and copper ions are positively charged species in solution, "affinity" is not likely. In *Ciccuttine*, zinc was used in the stromal cell culture medium because the stromal cells had been genetically modified with a plasmid containing SV40 T antigen (an immortalizing gene) driven by four metallothionein promoters (which are activated by the presence of zinc and when activated drive expression of the immortalizing SV 40 large T). For these reasons, the presence of zinc for proliferation of the **stromal** cell lines and removal of zinc for suppression of stromal cell line proliferation does not in any way teach or suggest the claimed invention, that reduction of copper is useful for *ex vivo* expansion of **hematopoietic** cells.

For these reasons, Applicants submit that neither *Moore* nor *De Bruyn*, alone or in combination with *Cicuittine* teaches or suggests the claimed method. Therefore, the rejection should be withdrawn.

II. The Claims are Not Obvious over *Moore* or *De Bruyn* in view of *Percival*

Claims 6-7 and 38-39 were also rejected under 35 U.S.C. § 103(a) over *Moore* or *DeBruyn* each in view of of *Percival* et al. J. Nutrition 122: 2424-2429 (1992) ("*Percival*"). The content of *Moore* and *De Bruyn* is discussed above in the first rejection under 35 U.S.C. § 103(a). The Examiner asserts that *Percival* teaches culture conditions that will stimulate growth while inhibiting differentiation, particularly pointing out the abstract of Percival and page 2428. Applicants traverse.

Percival does not cure the fatal deficiencies of *Moore* and *De Bruyn.* First, the instant specification expressly excludes HL-60 cells (*See*, specification at page 25, lines 22-25). HL-60 is a cell line that could not be isolated from a donor or patient, as the claims require, as it is a cell line known to propagate only *in vitro*. More importantly, no conditions that stimulate growth or inhibited differentiation could be provided to a leukaemic cell line such as HL-60. These cells proliferate continuously in culture with no need of cytokines support, and these cells do not need

to be provided with specific factors for the inhibition of their differentiation. These cells, by definition, are blocked in their ability so undergo "spontaneous" differentiation.

More specifically, HL-60 cells can be induced to differentiate with a variety of compounds and this may result in decreases of SOD activity that accompanied differentiation of K562 cell line. It is necessary then, in this model, to determine whether incubating the HL-60 cells with the copper chelating compound would result in differentiation following a subsequent loss of Cu/Zn-SOD activity. For this purpose, *Percival* used a copper chelator to reduce SOD activity and to test if the reduction of SOD activity may induce leukaemic cell differentiation. However, the reduction of SOD activity did not induce leukaemic cell differentiation. The reduction of copper resulted in the lowering of SOD activity but was without any effect on cell differentiation (*See*, *Percival* at page 2428, first column). When these leukaemic cell lines are induced to differentiate, they lose their unlimited ability to proliferate. Therefore, it was claimed in the paper that the reduction of cellular copper by the copper chelators does not induce differentiation or inhibit cell proliferation.

Percival summarizes her study by expressly stating that reduction of copper using TEPA resulted in no alteration in the stage of differentiation, thereby teaching away from the instant invention (*See*, *Percival* at page 2428, column 2, last full paragraph):

> "In summary, incubating HL-60 cells with TEPA resulted in copper-deficient cells without loss of viability or alteration in the stage of differentiation."

Furthermore, HL-60 cells are committed (i.e. differentiated) cells and not stem or progenitor (i.e. non-differentiate) cells and hence HL-60 cells cannot serve as a model to determine or predict the effect of copper chelators on hematopoietic stem cells and/or progenitor cells. As such, HL-60 cells do not provide motivation to conduct these undue experiments.

For the reasons set forth above, and because no effect of copper chelation on the inhibition of cell differentiation, proliferation, etc., could be inferred from *Percival* (Percival, in fact, teaches away from the effect of copper chelators on cell proliferation and differentiation), the ordinarily skilled artisan would not and could not combine *Percival* with either of *Moore* or *De Bruyn* to achieve the claimed invention. Thus, Applicants request this rejection be withdrawn.

CONCLUSION

On the basis of the foregoing amendments, Applicants respectfully submit that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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